

Adjuvant radiotherapy for breast cancer significantly improves overall survival: the missing link[☆]

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Abstract

Background and purpose: The influence of surgical adjuvant radiotherapy on overall survival of patients with operable breast cancer is still a controversial subject. The negative result of the EBCTCG meta-analysis (Early breast cancer trialists', collaborative group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomised trials. *N. Engl. J. Med.* 1995;333:1444–1455) of clinical randomized trials on adjuvant radiotherapy in breast cancer is in strong contrast with the Danish 82B, 82C and British Columbia trials (Overgaard M, Hanse PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N. Engl. J. Med.* 1997;337:949–955; Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomized trial. *Lancet* 1999;353:1641–1648; Ragaz J, Jackson S, Le N, et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N. Engl. J. Med.* 1997;337:956–962) showing an impressive survival benefit. This paper tries to fill in the gap between the conflicting results.

Materials and methods: The 36 trials of the EBCTCG (Early breast cancer trialists', collaborative group, 1995) were prospectively screened for a number of objective parameters that are usually not analyzed in review papers. The odds of death data (and its variance) were borrowed from the original meta-analysis (Early breast cancer trialists', collaborative group, 1995) to check whether the objective features were significant predictors for overall survival benefit.

Results: A significant survival benefit for the radiotherapy arm was found for recent trials ($2P < 0.05$), large trials ($2P < 0.03$), trials that used standard fractionation ($2P < 0.02$), and trials with a favourable crude survival ($2P < 0.03$). For these four parameters clear parameter-effect relations were found. In recent and large trials the odds reduction was 12.4% ($2P = 0.004$).

Conclusions: Surgical adjuvant radiotherapy significantly improves overall survival of breast cancer patients provided that current techniques are used and treatment is given with standard fractionation. For the best subgroups we observed an odds of death reduction of more than 20%. The results of this study stress the importance of reducing cardiovascular and other late toxicity in adjuvant radiotherapy for breast cancer. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Adjuvant radiotherapy; Breast cancer; Overall survival; Prognostic factors; Meta-analysis; Review

1. Introduction

For many years there exists controversy about the survival benefit of surgical adjuvant radiotherapy for breast cancer [1,24]. Based on the paradigm, proposed in the 1980s, that operable breast cancer is a systemic disease [15], no survival benefit due to a local-regional treatment

can be expected. On the other hand, more recent developments in the field of breast cancer screening, long term follow-up studies of breast cancer [19,23,24,27,40,43] and especially some trials on adjuvant radiotherapy underline the curability of breast cancer and the importance of local-regional relapse in the development of metastasis, for part of the patients. The most recently quoted radiotherapy studies (DBCG [30,31] and BCCA [37,38]) even show an impressive significant overall survival benefit in the radiotherapy group. The controversy however remains since an overview [9] of all properly executed clinical randomized trials on adjuvant radiotherapy for breast cancer showed a clinically important reduction in local recurrence in the radiotherapy group (odds ratio 0.33 ± 0.03) but failed

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to demonstrate a significant overall survival benefit (odds ratio 0.974 ± 0.025). The goal of this paper is precisely to fill in the missing link between the latter negative result and the significant benefits in individual trials.

We therefore explore the trials analyzed by the EBCTCG to discover essential mutual differences between the trials, based on hypotheses (pointing to crucial determinants for the effect of adjuvant radiotherapy) postulated in the literature. Although the importance of the EBCTCG paper is abundantly clear, we should realize that it discusses a motley mixture of trials, differing in techniques, indications, target volumes, systemic therapies, types of surgery, fractionation, It is precisely this heterogeneity in the trials that allows us to efficiently compare subgroups of trials with at least one common characteristic. Using the kind of generalizing inherent to a meta-analysis might very well hide even a large benefit of nowadays adjuvant radiotherapy

behind the detrimental effects of formerly used irradiation techniques. This is supported by the emerging data on increased non-breast cancer mortality [6,9,20,25,39,44].

2. Materials and methods

We performed this analysis on the randomized clinical trials comparing radical or breast conserving surgery with (in the study group) and without (in the control group) adjuvant radiotherapy (Table 1). Limiting our list to the trials in the EBCTCG report [9] gives the advantage of uniform and simple handling of all studies, using the data (odds minus expected and variance) from the EBCTCG report. In the second place, direct comparison between our results and these of the EBCTCG can be done, with the emphasis on the fact that both results originate from the same clinical

Table 1

List of analyzed randomized clinical trials comparing surgery for operable breast cancer with the same surgery followed by adjuvant radiotherapy, ordered following begin year of trial and number of patients^a

Trial	Y	P	Fr. dose (Gy)	Dose intensity	M (%)	Syst.	Odds ratio (confidence interval)	Odds reduction ± 1 SD (%)
Berlin-Buch ABC	62	255		9.6	79	None	1.22 (0.91–1.64)	-22.2 \pm 16.5
Oslo X-ray	64	552		7.0	57	Endoc.	1.03 (0.82–1.29)	-2.6 \pm 11.9
Oslo Co-60	67	563			47	Endoc.	1.07 (0.83–1.36)	-6.7 \pm 13.0
Heidelberg XRT	69	143			82	None	1.36 (0.92–2.01)	-36.3 \pm 23.2
Manchester RBS1	70	714	2.73	13.7	61	Endoc.	0.90 (0.74–1.09)	10.0 \pm 9.4
Kings/Cambridge	70	2800			60	None	1.01 (0.92–1.12)	-1.3 \pm 5.1
SASIB	71	377	2.76	10.0	43	None	1.28 (0.92–1.77)	-27.9 \pm 18.7
NSABP B-04 ^b	71	717	2.00	10.0	54	None	0.87 (0.71–1.07)	12.7 \pm 9.8
Stockholm A ^b	71	1281	1.80	9.0	48	None	0.85 (0.69–1.04)	15.3 \pm 9.5
WSSA Glasgow	72	217	2.10	10.5	54	None	0.91 (0.62–1.33)	9.0 \pm 18.6
INT Milan 1	73	56			54	None	1.55 (0.72–3.33)	-55.2 \pm 48.9
Wessex	73	151	2.30	11.5	58	None	0.67 (0.44–1.04)	32.6 \pm 18.2
Mayo Clinic	73	241	2.08	6.7	56	Mixed	0.98 (0.68–1.40)	2.0 \pm 18.1
Edinburgh 1	74	348	4.30	10.8	38	None	0.99 (0.70–1.41)	1.0 \pm 17.8
Piedmont OA	75	280	1.58	7.9	57	Chemo.	1.13 (0.82–1.56)	-12.7 \pm 17.5
DFCI Boston	76	218	2.25	9.0	45	Chemo.	1.22 (0.80–1.84)	-21.6 \pm 23.3
Glasgow	76	219	2.53	12.7	58	Chemo.	0.90 (0.62–1.31)	9.6 \pm 18.0
SECSG1	76	256		10.0	44	Chemo.	0.76 (0.51–1.12)	24.0 \pm 17.4
NSABP B-06 ^b	76	1450	2.00	10.0	34	Chemo.	0.88 (0.71–1.10)	11.6 \pm 10.4
Düsseldorf U.	77	88	2.00	10.0	47	Chemo.	1.53 (0.76–3.08)	-52.7 \pm 44.6
Toronto-Edmont.	78	50	2.86	17.5	48	Mixed	0.83 (0.33–2.04)	17.4 \pm 42.0
MD Ander. 7730B	78	97	1.83	9.8	54	Chemo.	1.83 (1.01–3.32)	-83.2 \pm 41.6
BCCA Vancouver	78	318	2.50	13.3	32	Mixed	0.72 (0.48–1.08)	28.2 \pm 17.9
S Swedish BCG ^b	78	768	1.75	5.1	34	Mixed	0.95 (0.74–1.21)	5.3 \pm 12.4
Metaxas Athens	79	71	2.00	9.9	39	Mixed	0.48 (0.22–1.06)	52.2 \pm 28.6
Coimbra	79	124	3.00	9.0	55	Chemo.	1.20 (0.72–1.99)	-19.9 \pm 28.4
Scottish D	80	93	2.73	11.5	28	Endoc.	1.74 (0.80–3.81)	-74.3 \pm 53.3
Helsinki	80	99	3.00		31	Chemo.	1.44 (0.69–3.01)	-44.2 \pm 45.3
NSABC Israel	80	112	2.00	10.8	34	Chemo.	1.27 (0.66–2.46)	-27.0 \pm 38.1
Uppsala-Orebro	81	381	2.00	9.9	6	None	0.64 (0.28–1.44)	36.1 \pm 33.5
ECOG EST3 181	82	332	2.00	10.4	27	Mixed	1.04 (0.68–1.60)	-3.9 \pm 22.4
St George's	82	400	2.00	9.7	9	Mixed	1.15 (0.55–2.39)	-14.9 \pm 40.0
Danish BCG 82c post ^b	82	1267	2.00	10.0	25	Endoc.	0.97 (0.77–1.22)	3.4 \pm 11.6
Danish BCG 82b pre ^b	82	1520	2.00	10.0	19	Chemo.	0.77 (0.61–0.99)	22.7 \pm 10.9
BMFT 03 Germany	84	199	2.00	9.2	13	Chemo.	0.73 (0.33–1.62)	26.8 \pm 34.8
Ontario COG ^b	84	837	2.52	13.3	8	None	0.87 (0.54–1.39)	13.5 \pm 22.4

^a Y, begin year of trial; P, number of patients; Fr., fraction; M, mortality; Syst., common systemic therapy.

^b Trials remaining after exclusion of old and small trials (see text).

Table 2
List of objective features analyzed for influence on survival benefit

Year in which patient accrual started
Photon beam energy
Fraction dose
Overall treatment time
Radiotherapy dose intensity
Target volume: breast or thoracic wall, supraclavicular, axillar or internal mammary lymph nodes
Radiation dose delivered to the different parts of the target volume
Total number of patients in the trial
Total number of deaths in the trial
Percentage of deaths in the trial
Combination with adjuvant systemic therapy

data. For ease of referral the same abbreviations and definitions as in the EBCTCG report are used.

Each of the studies in Table 1 were characterized by a number of objective features (Table 2) for which an influence on treatment result can readily be expected. Most of them are biological or technical factors related to either the patient population, the trial or the radiotherapy. In this paper the influence of these factors on overall survival is investigated. We use the crude survival (% of deaths in the trial) as a surrogate for global prognosis of patients in the particular trial. If the trial includes low stage patients than the crude survival will be high and vice versa.

The statistical procedures are identical to these in the EBCTCG report. The odds ratios and odds reductions, including confidence intervals, are described in detail in the EBCTCG monograph [11] referring to [8,33,34]. A negative odds reduction means a benefit for the surgery only group. Statistical significance is calculated using log-rank statistics [11].

For factors that were found to affect overall survival, parameter-effect relations were explored. Based on these relations a selection of clinical trials that were supposed to be performed with adequate radiotherapy (in relation to overall survival benefit), was made. The characteristics of these trials were looked at in detail.

3. Results

The number of studies included in the EBCTCG analysis is 36 with a total number of patients treated of 17 273. At least 50 patients were treated in each trial. The largest trial contained 2800 patients. The trials started accrual between 1962 and 1984. Doses ranged from 25 to 65 Gy, given in 10–30 fractions over a time period of 16–55 days. Mean fraction dose of each trial varied between 1.5 Gy and 4.3 Gy. The photon beam energy analysis was restricted to three categories: orthovoltage, megavoltage or mixed therapy. Crude mortality rates varied between 6 and 82%. Adjuvant systemic therapy was associated in 24 of 36 trials (57% of patients).

In a univariate analysis, begin year of trial, number of

patients in the trial, fraction dose, and crude survival in the trial showed statistically significant results. Relevant data concerning these four parameters are summarized in Table 3. Obviously, for these characteristics clinical trends exist. The odds reductions and trends are illustrated in Figs. 1–4. Each of the figures has the same structure: part A compares subgroups fulfilling the criterion with the excluded trials (e.g. Fig. 1A: ‘trials that started after 1970’ compared with ‘trials that started in 1970 and earlier’) and estimates the odds reduction between the two subgroups (i.e. an estimate of gain in odds reduction using the ‘mean technique’ from after 1970 in comparison with the older techniques). From part A, the relevant break points can be derived (e.g. Fig. 3A: optimal fraction dose for adjuvant breast cancer irradiation seems to be at least 1.8 and maximally 2.5 Gy). Part B in each figure shows more clearly the existing trends.

The influence of the begin year of trial as a significant factor for survival benefit is illustrated in Fig. 1A. Numeric data are given in Table 3. For early trials there is a drawback of the applied radiotherapy. Opposed to that, the more recent the trial, the more the survival benefit of adjuvant radiotherapy is showing up. Comparing recent to former trials stresses the importance as prognostic factor: there is a gain in odds reduction of 21.1% ($2P < 0.02$) between trials started after 1980 and up to 1970.

The trend in Fig. 1B is significant ($2P = 0.02$). Over virtually the entire time era in which the trials started there is at least a trend (Fig. 1A), when testing the hypothesis that the odds reduction due to radiotherapy is larger in recent trials compared with older trials.

The number of patients accrued in the trial represents the second significant factor for survival benefit due to adjuvant radiotherapy (Fig. 2, Table 3). The big trials systematically produce a larger survival benefit than the small trials, with two-sided P -values achieving significance at lower than 200 (radiotherapy group significantly worse than surgery only) and around 600 (radiotherapy group significantly better than surgery only) patients in the trial (Fig. 2A). In most other points at least a trend is observed considering the hypothesis that radiotherapy produces a larger survival benefit in big trials compared with small trials. The trend in Fig. 2B is significant: $2P = 0.02$.

The third significant factor for overall survival benefit is fractionation. The analysis was done on the group of trials on which detailed fraction dose information is available (31 studies, 12 960 patients). The odds ratio of this group of trials, is 0.933 (0.88–0.99), $2P < 0.04$, in favour of radiotherapy. Detailed analysis reveals that this benefit is almost entirely due to the trials using ‘conventional’ (1.8–2.0 Gy/f) or ‘safe’ (1.8–2.5 Gy/f) fractionation (Table 3). Fig. 3A is mainly determined by the (large) group of trials using conventional fractionation. The apparent benefit for the high fraction dose group, at the highest cut-off, has no statistical nor clinical meaning (small number of patients). In Fig. 3B the parameter effect relation is presented. The main trial

Table 3
Summary of results and statistical significance of selected factors

Feature	Number of patients in the selection	Odds ratio	Confidence interval	Odds reduction (%)	P-value
<i>Begin year of trial</i>					
>1970	12567	0.935	1.00–0.88	6.5	0.048
>1980	4936	0.882	1.02–0.77	11.8	0.080
<i>Number of patients in the trial</i>					
>600	11354	0.932	0.99–0.88	6.8	0.028
<150	933	1.304	1.07–1.59	–30.4	0.008
<i>Fractionation (Gy/fraction)</i>					
All known	12960	0.933	0.88–0.99	6.7	0.034
≥1.8–≤2.0 ^a	7915	0.896	0.82–0.98	10.4	0.016
Other	5054	0.973	0.89–1.07	2.7	0.557
≥1.8 ≤2.5 ^b	9060	0.894	0.83–0.97	10.6	0.006
Other	3909	1.005	0.90–1.12	–0.5	0.931
<i>Crude survival</i>					
≥80%	3337	0.799	0.66–0.97	20.0	0.025
≤35%	398	1.272	1.01–1.61	–27.2	0.044
<i>Radiotherapy dose intensity (Gy/w)</i>					
≥12.6	2138	0.869	0.75–1.01	13.1	0.065
<i>Adjuvant systemic therapy</i>					
All types	10031	0.961	0.92–1.06	3.9	0.267
Chemo	4903	0.960	0.87–1.07	3.7	0.487
Other ^c	5128	0.963	0.87–1.05	4.1	0.385
None	7563	0.988	0.90–1.03	1.3	0.722
<i>Beam energy</i>					
Orthovolt	771	0.991	0.82–1.20	0.9	0.929
Megavolt	9699	0.990	0.92–1.06	0.9	0.795
Combined	6806	0.963	0.89–1.04	3.7	0.330
<i>Extension of radiotherapy target volume</i>					
Extended ^d	12750	0.962	0.91–1.02	3.8	0.167
Limited ^d	1776	1.122	0.97–1.29	–12.2	0.108

^a Classical fractionation.

^b Safe fractionation.

^c Hormonal or mixed hormono-chemotherapy.

^d Extended means comprehensive irradiation (all sites); limited means that one of the following sites is not irradiated: breast/thoracic wall or axilla/supraclavicular fossa or internal mammary node chain.

in the 'X' group is the King's trial (60% of all patients from the X group). Keeping in mind the applied hypofractionation in that trial [2], it seems fair to place it between the two most right subgroups, thereby confirming the existing relation for large fractions. The subgroups <1.8 Gy/f possibly illustrate radiation dose intensity effects (see below). For subgroups with ≥1.8 Gy/f (1.8–2.0/>2.0–<2.75/>2.75) a significant trend exist with $2P = 0.01$. Including the King's trial anywhere in the hypofractionation region strengthens the trend ($2P < 0.01$).

Fig. 4A demonstrates the increasing benefit as crude survival (prognosis) increases and absence of benefit as crude survival decreases. In the right part of the figure, the number of patients in the low crude survival group is too low to give a reliable prediction of the real clinical differ-

ence between the good and the bad prognostic group, despite the statistical significance of the result. At the left side of the Fig. 4A, the first significant point is reached at the crude mortality <20% with a patient number of 3337, allowing for a reliable prediction of the obtained survival benefit due to the radiotherapy and a reliable, significant difference with more benefit for the best prognostic groups. Split up in four intervals (Fig. 4B) a significant trend ($2P = 0.03$), in favour of good prognostic patients, is obtained.

Based on the above results we excluded old (≤1970) and small (≤400 patients) trials. A remainder of 7840 patients (44.6% of original number) were treated in the seven remaining trials (Fig. 5, group D). The global odds reduction (for overall survival) for the selection is $12.3 \pm 4.3\%$

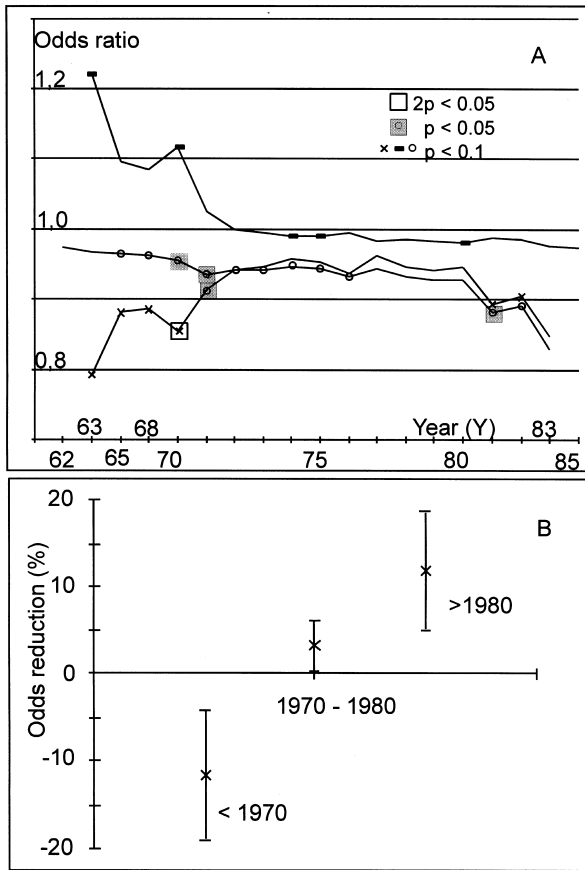


Fig. 1. Relation between begin year of trial and odds of death reduction (OR \pm 1 SD). (A) All years in which trials started; (–) combined result of all trials that started before indicated year; (o) combined result of all trials that started in the indicated year or later; (x) quotient of odds ratios o/–x denotes how much radiotherapy was better (i.e. $x < 1.0$) in recent trials compared with older ones. Framed tick marks: $2P < 0.05$ (two-sided testing), shaded tick marks: $P < 0.05$ (one-sided testing), other tick marks: $P < 0.1$ (one-sided testing). (B) A partition is made with trials starting accrual before 1970, from 1970 to 1980, and after 1980.

($2P = 0.004$). The odds reduction for the eliminated population is $-2.0 \pm 3.1\%$ ($2P = 0.5$) (Fig. 5, groups A, B and C).

All of the seven trials in the selection have a positive overall survival effect for the irradiated groups, some of which are highly significant. The odds reduction for each of the selected trials except one is at least 11.6%, when taking the Danish pre- and postmenopausal trials together. The exception (odds reduction of 5.3%) is a trial with a very low dose intensity (5.1 Gy/w). On the other hand, all of the selected trials used close to safe fractionation (1.75–2.52 Gy/fraction). The influence of prognosis represented by crude survival is less clear in this selection of trials, although the patients in trials with low ($\leq 20\%$) crude mortality took more advantage from radiotherapy (overall survival odds reduction = 20.8%, $P < 0.04$) than those in the subgroup of trials with high ($> 20\%$) crude mortality (odds reduction = 10.4%, $2P < 0.03$). The small overall

disadvantage (only 12 out of 29 trials have a survival benefit) for the irradiated patients in the eliminated trials (old or small) is almost entirely due to the trials who are both old and small (odds reduction of -11.7% , none out of these four trials has a survival benefit, Fig. 5 group A).

Although no significant influence on survival could be demonstrated for overall treatment time, total dose, radiotherapy target volume, photon beam energy and associated systemic therapy, some additional results are worthwhile to be mentioned (Table 3).

In the overall treatment time analysis a significant benefit for the radiotherapy groups was obtained for all ten trials that treated patients (7369) in 35–38 days: odds ratio = 13.6 ± 4.3 ($2P = 0.005$). Thirty-five to 38 days correspond (except one small study with a negative result and 2.25 Gy per fraction) with a dose of 50 or 54 Gy in 2 or 45 Gy in 1.8 Gy fractions five times a week, thus overlapping with the ‘classical fractionation’ group. All of these trials had an advantage for the radiotherapy group. The patients treated in these ten trials had significantly more

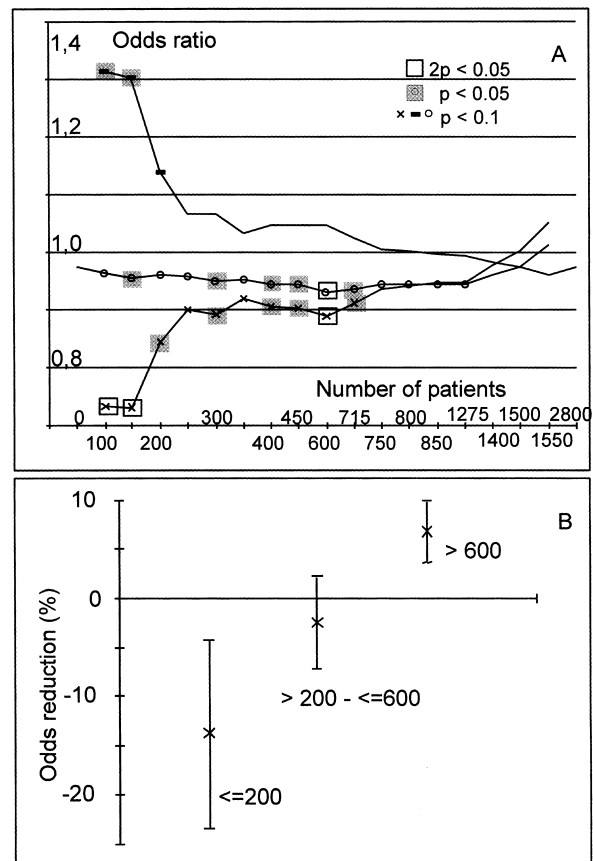


Fig. 2. Relation between total number of patients and odds of death reduction. (A) Detailed presentation; (–) combined result of all trials that accrued less than indicated number of patients; (o) combined result of all trials that accrued at least indicated number of patients; (x) quotient of odds ratios o/–x denotes how much radiotherapy was better (i.e. $x < 1.0$) in large trials compared with small ones. (B) The groups represent trials with up to 200 patients, 201–600 patients, and at least 600 patients (OR \pm 1 SD).

benefit of radiotherapy compared with the patients in the other trials ($2P = 0.003$).

For total dose no trend could be observed either, but the trials treating with 50–54 Gy are very well in agreement with those treating in 35–38 days, and therefore show comparable results (odds reduction in favour of radiotherapy: 11.1 ± 4.4 , $2P = 0.01$).

For the ratio of total dose and overall treatment time (dose intensity) a trend in favour of high dose intensity can be seen (Table 3). The statistical significance is borderline but for every cut off point a benefit is seen for the high dose intensity group compared with the low dose intensity group (data not shown).

Extension of the target volume (internal mammary node chain + supraclavicular fossa + thoracic wall or breast) does not lead to clear trends, although the radiotherapy arm in trials with extended target volume did significantly

better than in trials irradiating only two of the three parts of the extended target volume ($2P < 0.05$). The omitted group of trials in this comparison (the trials treating only one part of the extended target volume) consists primarily of the breast conserving trials where radiotherapy is given on the remaining breast tissue, which are not to be compared with trials on radiotherapy after mastectomy (relating to target volume).

As a last result, no influence of systemic adjuvant therapy could be found in our analysis (Table 3): none of the subgroups related to systemic adjuvant therapy shows a clinically or statistically relevant advantage or disadvantage ($2P > 0.2$).

4. Discussion

Although the original meta-analysis [9] does not show a significant (neither clinically, nor statistically) benefit for adjuvant radiotherapy, classifying the studies following a

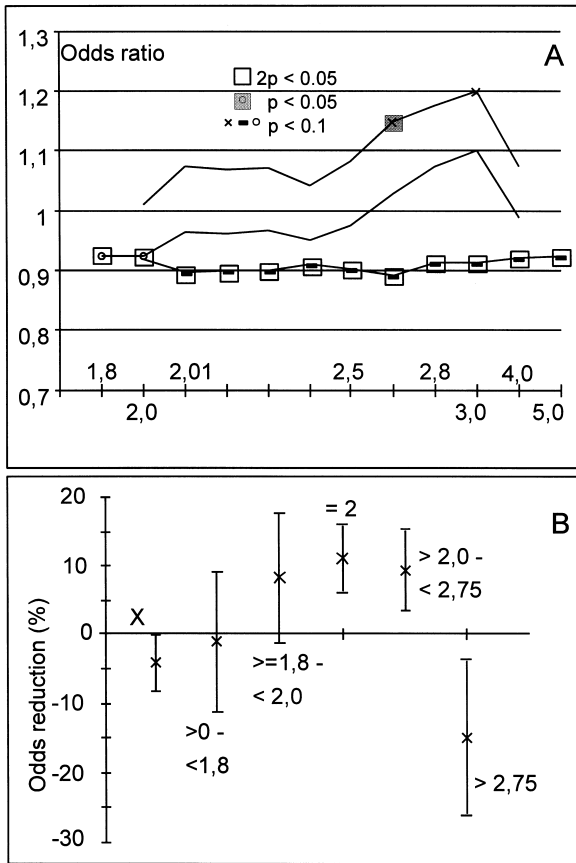


Fig. 3. Relation between used fraction dose and odds of death reduction in the conventional to hypofractionation interval (i.e. fraction dose ≥ 1.8 Gy). (A) Detailed presentation; (–) combined result of all trials that used fractions less than indicated fraction dose; (o) combined result of all trials that used fractions at least indicated fraction dose; (x) quotient of odds ratios $o/-x$ denotes how much radiotherapy was worse (i.e. $x > 1.0$) in trials using large fractions compared with trials using small fractions. (B) The fraction intervals (expressed in Gy) are placed next to the resulting odds reduction (OR ± 1 SD). The subgroup characterized with X represents the group of trials where incomplete data on fraction size were found.

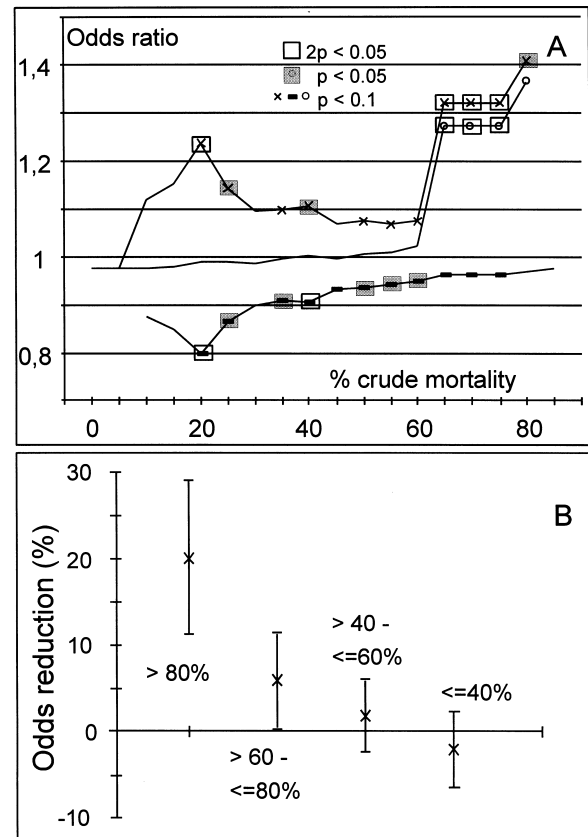


Fig. 4. Relation between crude survival of patients in the trial and odds of death reduction. (A) Detailed presentation; (–) combined result of all trials with crude mortality less than indicated percentage; (o) combined result of all trials with crude mortality at least indicated percentage; (x) quotient of odds ratios $o/-$. The inverse of x ($= 1/x$) denotes how much radiotherapy was more effective (i.e. $1/x > 1.0$) in high crude survival trials compared with low crude survival ones. (B) Trials were divided in four subgroups following crude survival in the trial, respectively $>80\%$, $>60 - \leq 80\%$, $>40 - \leq 60\%$, and $\leq 40\%$ (OR ± 1 SD).

number of objective characteristics leads to significant differences in treatment outcome. This contrasts with the absence of ‘statistical’ heterogeneity in the dataset [9], but the test that was used to detect heterogeneity is an insensitive one [11]. The numeric values of the significance are not thrilling, but as far as we know this is the first meta-analysis that provides strong evidence that adjuvant radiotherapy significantly improves overall survival and explains why some studies do and others don’t show the expected survival benefit.

Our analysis was not done on the individual patient data, but it has the advantage of performing an ‘intention to treat analysis’ where the influence of patient based adaptations is eliminated. The characterization of each of the trials was done in a systematic way and before any of the results were known. At the time that the significant results became visible, a check to exclude erroneous characterization of the trials was done without revealing mistakes. The major statistical flaw in this analysis is the division in subgroups (see part B of Figs. 1–4). We therefore included the complete statistical data in parts A of each figure. On the other hand, the group of 36 trials carries in itself the information for the clinical cut offs. There is no reason why the clinically relevant cut offs should correspond to statistically acceptable intervals.

Relating to the begin year of patient accrual in the trial, a significant benefit for overall survival is shown for recent studies (>1970, Table 2). The difference between recent and older trials illustrates that the radiotherapy with older and with newer techniques have to be considered as two different treatments, and should not be included in one meta-analysis. It is likely that the omission of simulation prior to radiotherapy, the absence of computerized tomography for planning purposes and computer planning with tissue heterogeneity correction, results in significant differ-

ence in target volume coverage and induced normal tissue toxicities, especially cardiovascular damage, and subsequent mortality. One might object that the follow-up time of some of the trials is not long enough to show this cardiovascular mortality, but the updates from the DBCG 82b [30] and 82c [31] as well as the BCCA [38] and NSABP-B04 [16] and -B06 [17,12] trials showed statistically and clinically more convincing results than the early publications, respective [7,13,14,29,37]. The same is true for the EBCTCC analysis itself [9,11]! Moreover, including updated information (longer follow-up) of the DBCG 82B and 82C will result in increased survival benefit for radiotherapy, due to increased statistical weighing of these studies (the consequence of the number of events and the latent period of several years of follow-up before a survival difference is seen in both trials [30,31]).

The importance of techniques is further illustrated in an analysis of all randomized clinical trials in early breast cancer comparing extended surgery to limited surgery plus adjuvant radiotherapy [45,46]. It is remarkable that for both sets of trials, the year 1970 is the breaking point in terms of odds reduction [45,46].

Small scale trials can lead to unreliable results or absence of significant results due to lack of power of the trial [3,4,42]. In the EBCTCG analysis there were 10 (!) studies with less than 150 patients with a combined odds ratio of 1.304, $2P = 0.008$ (i.e. 30% increased mortality in the radiotherapy group). In eight of these the radiotherapy has a negative effect on overall survival of the irradiated patients. With increasing number of patients, the survival benefit increases too (Fig. 2). In eight of nine trials with more than 600 included patients, there is a clinical benefit (the other one showing only a small disadvantage for the radiotherapy group: odds ratio = 1.013, $2P = 0.79$). At the same breakpoint (600 patients) the survival benefit reaches significance (Table 3). The poorer results in small trials are possibly related to suboptimal equipment and lack of expertise of the participating centres. If accrual drops below a few patients per year, this can cause problems with experience of the radiotherapy department. This phenomenon is well known for surgery in rectal cancer: the number of patients operated on by the surgeon is a significant prognostic factor [26,35]. More recently ‘experience’ or ‘included patients in a trial’ was a significant factor for treatment outcome due to chemotherapy in a multicentre EORTC trial [5]. More support in favour of specialized centres, with updated equipment, can be found in the EURO CARE study where more than 20% survival difference has been found between different cancer centres with the explicit observation that poorest centres did worse [36].

The third factor is related to the radiotherapy protocols: fraction dose. It is sufficiently proven that large fraction doses result in a larger amount of late damage than of early reactions and tumour control [41]. The finding that patients treated with large fraction dose have a smaller survival benefit, compared with conventional fraction dose therapy, is in

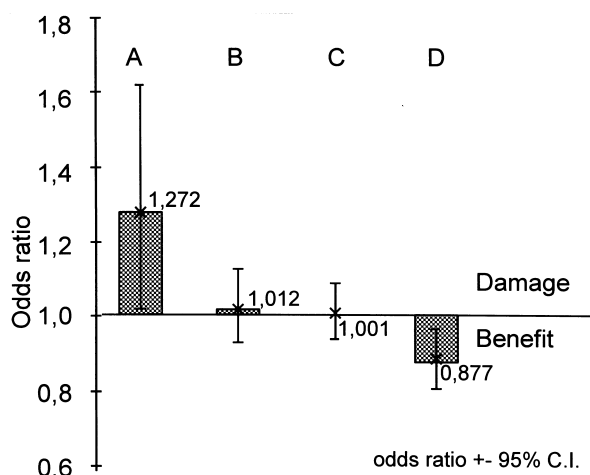


Fig. 5. Bivariate representation of the influence of begin year and number of patients in the trial. Selection of trials: (A) ≤ 1970 and ≤ 400 patients; (B) ≤ 1970 and > 400 patients; (C) > 1970 and ≤ 400 patients; (D) > 1970 and > 400 patients. Represented is odds ratio and 95% confidence intervals.

Table 4
Influence of prognosis (parameter = N-stage) on reduction of mortality (at 10 years of follow-up), illustrated in individual studies^a

Study	Overall survival	CT (%)	CT + RT (%)	BCS (%)	BCS + RT (%)	Reduction in mortality (ratio)
Danish BCG 82b [30]	pN0	70	82			0.60
	1–3 nodes	54	62			0.82
	≥4 nodes	20	32			0.85
BCCA Vancouver [37] (Dr J. Ragaz, personal communication) ^b	1–3 nodes	68	77			0.72
	≥4 nodes	37	46			0.86
NSABP-B06 [17]	pN0 ^c			77	83	0.73
	pN1 ^c			60	68	0.80

^a CT, chemotherapy; RT, radiotherapy; BCS, breast conserving surgery.

^b These results were confirmed in the update of the study [38].

^c Overall survival is at 8 years.

agreement with the results of cause of death analyses [6,9] and studies of cardiac toxicity after adjuvant radiotherapy for breast cancer [20,39,44]: reducing the biological damage to the heart by reducing the fraction dose must lead to increased survival benefit, as shown in the DBCG trials [25]. The importance of fraction dose was shown equally in our analysis of trials comparing extended surgery vs. limited surgery plus adjuvant radiotherapy [45,46].

A last key to overall survival benefit is the prognosis of patients. We found an influence of this factor in the univariate analysis (Table 3), in the parameter effect relations (Fig. 4), and in the selection of trials (see results). The importance of this factor is supported by analysis of individual trials. In Table 4 the Danish 82B [30], the British Columbia [37], and the NSABP-B06 study [17] illustrate the larger odds reduction by adjuvant radiotherapy for the best prognostic groups. As a measure for odds of death reduction we took the reduction in overall mortality at 10 (8) years. Analogue trends were seen in the disease free survival for the above mentioned studies. These data can be completed with the results from the Glasgow study [28] where the ratio (adjuvant radiotherapy vs. no radiotherapy) in percentage relapse of disease at 10 years was 0.75 in the 1–3 nodes group compared with 0.85 in the ≥4 nodes group. This effect was also present, be it less pronounced, in the NSABP-B02 study but was not noticed at the time of the original publication [18]. The ratio in percentage NED at 5 years follow up (adjuvant radiotherapy vs. no radiotherapy) was 0.88 in the 1–3 nodes group compared with 0.92 in the ≥4

nodes group. Table 4 can be compared with Table 5 where the data of 10 years overall mortality reduction by systemic adjuvant therapies are given. The contrast between Tables 4 and 5 is clear: systemic adjuvant therapies do not show the influence of prognosis on the amount of odds reduction (or reduction in overall mortality). This reflects a different biological working principle for adjuvant radiotherapy compared with systemic therapies. The observation that adjuvant radiotherapy has more effect on survival in the best prognostic groups was withheld by the post-mastectomy radiotherapy consensus panel (ASTRO Fall Symposium, Pittsburgh, PA, 1998 [22]).

After exclusion of old or small trials still about half of patients remain in the analysis. This is contradictory to the special effort of the EBCTCG to gather all executed trials including the small ones that have not been accepted for publication but that could give interesting information. Indeed it seems that these small trials do teach us something, especially about methodological problems, but not about the effect of adjuvant radiotherapy. The most reliable results concerning adjuvant radiotherapy are fairly obvious to be found in the larger trials. It is striking that all of the seven trials in the selection have a survival benefit with an odds reduction close to 13%. Comparison of some of these individual trials (see Table 4) with the results in Table 5 even shows a reduction in overall mortality at 10 (or 8) years of follow-up by radiotherapy, which is comparable with the reduction obtained by adjuvant chemo- or hormonal therapy.

Probably not coincidentally the trials all used a safe fractionation dose. The influence of dose intensity is supported by one trial using a low dose intensity of 5.1 Gy/w resulting in an odds reduction of only 5.3%. In the other six trials patients were treated at 9.0–13.3 Gy/w.

From the non-significant factors from Table 1 we retain the absence of influence of adjuvant systemic therapy. None of the different types of systemic adjuvant therapy brought along a (clinical or statistical) difference in effect of adjuvant radiotherapy. This is different from what is generally

Table 5
Reduction in mortality due to hormonal and cytostatic adjuvant therapies (ratio)

EBCTCG-overview [10]	Tamoxifen	Ovarian ablation	Chemotherapy
pN0	0.88	0.83	0.89
pN1	0.86	0.82	0.89

expected. Neither in the selection of recent and large trials an influence of adjuvant systemic therapy could be seen ($2P = 0.7$).

The significance of radiotherapy dose intensity (Table 3) is less pronounced and less clear. This phenomenon is well described for head and neck cancer, uterine cervix cancer, and others [21,32,41], and the same biological fundamentals (repopulation, [41]) are applicable to breast tumours. Although for every cut-off point the odds of death reduction is larger in the high dose intensity group than in the low intensity group (data not shown), this effect cannot be seen independently from the observation that best results were seen in the classical fractionation trials or 50–54 Gy trials (35–38 days overall treatment time). On the other hand, individual studies looking for effects of overall treatment time struggle with patient dependent gaps, opposite to our analysis which is an intention to treat analysis. We therefore propose to avoid gaps during adjuvant radiotherapy for breast cancer.

The benefit in terms of overall survival obtained due to radiotherapy in large trials, trials using ‘safe fractionation’, trials with high crude survival indicates in the first place that adjuvant radiotherapy improves overall survival. The only way to explain this is to accept that local-regional relapse can generate ultimately lethal distant disease. In the strict sense of the word, this does not preclude that breast cancer is a systemic disease, but it further supports the importance of local-regional control.

Our findings are in agreement with these of Koscielny [27] and Fortin [19] stating that local failure too should be considered as a source for new distant metastasis and subsequent mortality. Further, the highest probability of not yet microscopically disseminated breast cancer will be found in these patients with the best prognosis, which again is compatible with our results (influence of prognosis) and with the results in individual trials (Table 4). At last, our results illustrate that local-regional control and overall survival are two different end points in early breast cancer treatment, linked by local-regional relapse but separated by normal tissue toxicity and prognosis of patients. It will be the task of everyone involved in breast cancer treatment to better identify these subgroups of patients that benefit most from adjuvant radiotherapy not only in terms of prevention of local-regional relapse but also in overall survival.

5. Conclusion

Surgical adjuvant radiotherapy significantly improves overall survival and the highest relative benefit can be expected for best prognostic patients. The benefit is probably only present when heart sparing techniques and optimal fractionation doses are used. Under optimal conditions the odds of death reduction and observed 10 year mortality reduction due to adjuvant radiotherapy can be expected to be at least 20%.

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